Answer 1:

Bibliographic Information

The use of steroid sulfatase inhibitors as a novel therapeutic strategy against hormone-dependent endometrial cancer.
Foster, Paul A.; Woo, L. W. Lawrence; Potter, Barry V. L.; Reed, Michael J.; Purohit, Atul. Endocrinology and Metabolic Medicine and Sterix Limited, Faculty of Medicine, Imperial College London, St. Mary's Hospital, London, UK. Endocrinology (2008), 149(8), 4035-4042. Publisher: Endocrine Society, CODEN: ENDOAO ISSN: 0013-7227. Journal written in English. CAN 149:191352 AN 2008:932552 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The past few years have seen an increase in the reported incidence of endometrial carcinoma, one of the most frequently diagnosed malignancies of the female genital tract. Estrogen prodn. is vital for the mitogenesis of endometrial tumors. Inhibition of steroid sulfatase (STS), an enzyme responsible for the synthesis of steroids with estrogenic properties, may represent a novel therapeutic target for this type of cancer. This study investigates the effects of STX64 (also known as 667Coumate and BN83495) and STX213, two potent STS inhibitors, on hormone-dependent endometrial cancer cell growth in vivo. When tested in intact mice with endometrial cancer xenografts, STX64 had limited effect on tumor growth. In contrast, the microtubule disruptor STX140 reduced tumor growth by 55%. In a hormone-dependent endometrial xenograft model in ovariectomized mice, both STX64 and STX213 given orally, daily at 1 mg/kg significantly inhibited tumor growth by 48 and 67%, resp. However, when given orally at 1 mg/kg once weekly, only STX213 still inhibited tumor proliferation. At a higher dose of STX64 (10 mg/kg, orally, daily), a greater tumor growth inhibition of 59% was obsd. Liver and tumor STS activity was completely inhibited in all daily treatment groups. Plasma estradiol (E2) levels were also significantly decreased. A significant correlation was obsd. between plasma E2 concns. and STS activity, indicating the importance of circulating E2 on tumor growth. This novel study demonstrates for the first time that STS inhibitors are potent inhibitors of endometrial cancer growth in nude mice.

Answer 2:

Bibliographic Information

Progestin-Dependent Progression of Human Breast Tumor Xenografts: A Novel Model for Evaluating Antitumor Therapeutics.
Liang, Yayun; Besch-Williford, Cynthia; Brekken, Rolf A.; Hyder, Salman M. Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO, USA. Cancer Research (2007), 67(20), 9929-9936. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 147:445070 AN 2007:1174370 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Recent clin. trials indicate that synthetic progestins may stimulate progression of breast cancer in postmenopausal women, a result that is consistent with studies in chem.-induced breast cancer models in rodents. However, progestin-dependent progression of breast cancer tumor xenografts has not been shown. This study shows that xenografts obtained from BT-474 and T47 Da human breast cancer cells without Matrigel in estrogen-supplemented nude mice begin to regress within days after tumor cell inoculation. However, their growth is resumed if animals are supplemented with progesterone. The antiprogestin RU-486 blocks progestin stimulation of growth, indicating involvement of progesterone receptors. Exposure of xenografts to medroxyprogesterone acetate, a synthetic progestin used in postmenopausal hormone replacement therapy and oral contraception, also stimulates growth of regressing xenograft tumors. Tumor progression is dependent on expression of vascular endothelial growth factor (VEGF); growth of progestin-dependent tumors is blocked by inhibiting synthesis of VEGF or VEGF activity using a monoclonal anti-VEGF antibody (2C3) or by treatment with PRIMA-1, a small-mol. compd. that reactivates mutant p53 into a functional protein and blocks VEGF prodn. These results suggest a possible model system for screening potential therapeutic agents for their ability to prevent or inhibit progestin-dependent human breast tumors. Such a model could potentially be used to screen for safer antiprogestins, antiangiogenic agents, or for compds. that reactivate mutant p53 and prevent progestin-dependent progression of breast disease.

Answer 3:

Bibliographic Information

A therapeutic model for advanced endometrial cancer: Systemic progestin in combination with local adenoviral-mediated progesterone receptor expression. Dai, Donghai; Albitar, Lina; Nguyen, Tan; Laidler, Laura L.; Singh, Meenakshi; Leslie, Kimberly K. Reproductive Molecular Biology Laboratory, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of New Mexico Health Sciences Center, Albuquerque, NM, USA. Molecular Cancer Therapeutics (2005), 4(1), 169-175. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 142:233519 AN 2005:45906 CAPLUS

Abstract

Cancer of the uterine endometrium is a frequent gynecol. malignant disease for which few therapeutic options are available for advanced disease. Progesterone is the normal female hormone that limits growth and proliferation of endometrial cancers; however, progesterone receptors are frequently down-regulated, leading to treatment failures. The current studies explored the effectiveness of adenoviral-mediated progesterone receptor gene transduction in combination with progestin therapy in mouse xenograft models. Pretreatment of cells with progesterone receptor-encoding adenovirus and progestin inhibited the development of s.c. tumors in athymic mice. In the i.p. xenograft model, replacement of both isoforms of progesterone receptor, PRA and PRB, in combination with progestin treatment resulted in a significant 2.6-fold increase in overall survival time compared with control animals. These studies indicate that when progesterone receptor levels are maintained, progestin therapy is effective in limiting tumor growth. Future therapeutic regimens targeted at enhancing progesterone receptor expression have the potential to improve outcomes in women with endometrial cancer.

Answer 4:

Bibliographic Information

EM-652 (SCH 57068), a third generation SERM acting as pure antiestrogen in the mammary gland and endometrium. Labrie, Fernand; Labrie, Claude; Belanger, Alain; Simard, Jacques; Gauthier, Sylvain; Luu-The, Van; Merand, Yves; Giguere, Vincent; Candas, Bernard; Luo, Shouqi; Martel, Celine; Singh, Shankar Mohan; Fournier, Marc; Coquet, Agnes; Richard, Virgile; Charbonneau, Ronald; Charpenet, Gilles; Tremblay, Andre; Tremblay, Gilles; Cusan, Lionel; Veilleux, Raymonde. Oncology and Molecular Endocrinology Research Center, Centre Hospitalier Universitaire de Quebec (CHUQ), Pavilion CHUL, Department of Medicine, Laval University, Quebec, QC, Can. Journal of Steroid Biochemistry and Molecular Biology (1999), 69(1-6), 51-84. Publisher: Elsevier Science Ltd., CODEN: JSBBEZ ISSN: 0960-0760. Journal; General Review written in English. CAN 131:208327 AN 1999:437555 CAPLUS

Abstract

A review, with 224 refs. Breast cancer is the most frequent cancer in women while it is the second cause of cancer death. Estrogens are well recognized to play the predominant role in breast cancer development and growth and much efforts have been devoted to the blockade of estrogen formation and action. The most widely used therapy of breast cancer which has shown benefits at all stages of the disease is the use of the antiestrogen Tamoxifen. This compd., however, possesses mixed agonist and antagonist activity and major efforts have been devoted to the development of compds. having pure antiestrogenic activity in the mammary gland and endometrium. Such a compd. would avoid the problem of stimulation of the endometrium and the risk of endometrial carcinoma. We have thus synthesized an orally active non-steroidal antiestrogen, EM-652 (SCH 57068) and the prodrug EM-800 (SCH57050) which are the most potent of the known antiestrogens. EM-652 is the compd. having the highest affinity for the estrogen receptor, including estradiol. It has higher affinity for the ER than ICI 182780, hydroxytamoxifen, raloxifene, droloxifene and hydroxytoremifene. EM-652 has the most potent inhibitory activity on both ERα and ERβ compared to any of the other antiestrogens tested. An important aspect of EM-652 is that it inhibits both the AF1 and AF2 functions of both ERα and ERβ while the inhibitory action of hydroxytamoxifen is limited to AF2, the ligand-dependent function of the estrogen receptors. AF1 activity is constitutive, ligand-independent and is responsible for mediation of the activity of growth factors and of the ras oncogene and MAP-kinase pathway. EM-652 inhibits Ras-induced transcriptional activity of ERα and ERβ and blocks SRC-1-stimulated activity of the two receptors.

EM-652 was also found to block the recruitment of SRC-1 at AF1 of ERβ, this ligand-independent activation of AF1 being closely related to phosphorylation of the steroid receptors by protein kinase.

Most importantly, the antiestrogen hydroxytamoxifen has no inhibitory effect on the SRC-1-induced ERβ activity while the pure antiestrogen EM-652 completely abolishes this effect, thus strengthening the need to use pure antiestrogens in breast cancer therapy in order to control all known aspects of ER-regulated gene expression. In fact, the absence of blockade of AF2 by hydroxytamoxifen could explain why the benefits of tamoxifen obsd. up to 5 yr become neg. at longer time intervals and why resistance develops to tamoxifen. EM-800, the prodrug of EM-652, has been shown to prevent the development of dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma in the rat, a well-recognized model of human breast cancer. It is of interest that the addn. of dehydroepiandrosterone, a precursor of androgens, to EM-800, led to complete inhibition of tumor development in this model. Not only the development, but also the growth of established DMBA-induced mammary carcinoma was inhibited by treatment with EM-800. An inhibitory effect was also obsd. when medroxyprogesterone was added to treatment with EM-800. Uterine size was reduced to castration levels in the groups of animals treated with EM-800. An almost complete disappearance of estrogen receptors was obsd. in the uterus, vaginum and tumors in nude mice treated with EM-800. EM-652 was the most potent antiestrogen to inhibit the growth of human breast cancer ZR-75-1, MCF-7 and T-47D cells in vitro when compared with ICI 182780, ICI 164384, hydroxytamoxifen, and droloxifene. Moreover, EM-652 and EM-800 have no stimulatory effect on the basal levels of cell proliferation in the absence of E2 while hydroxytamoxifen and droloxifene had a stimulatory effect on the basal growth of T-47D and ZR-75-1 cells. EM-652 was also the most potent inhibitor of the percentage of cycling cancer cells.

When human breast cancer ZR-75-1 xenografts were grown in nude mice, EM-800 led to a complete inhibition of the stimulatory effect of estrogens in ovariectomized mice while tamoxifen was less potent and even stimulated the growth of the tumors in the absence of estrogens, thus illustrating the stimulatory effect of tamoxifen on breast cancer growth. When incubated with human Ishikawa endometrial carcinoma cells, EM-800 had no stimulatory effect on alk. phosphatase activity, an estrogen-sensitive parameter. Raloxifene, droloxifene, hydroxytoremifene and hydroxytamoxifen, on the other hand, all stimulated to various extent, the activity of this enzyme. The stimulatory effect of all four compds. was blocked by EM-800, thus confirming their estrogenic activity in human endometrial tissue. When administered to ovariectomized animals, EM-800 prevents bone loss, the effect on bone mineral d., trabecular bone vol., and trabecular sepn. being 5-10 times more potent than raloxifene. EM-800 lowers serum cholesterol and triglyceride levels in the rat as well as in women. In a Phase II study performed in patients with breast cancer showing failure on tamoxifen, 1 patient had a complete response while 5 patients had a partial response and stable disease for at least three months has been obsd. in an addnl. 13 patients for a total of 19 pos. responses out of 43 evaluable patients (44.2%). No significant secondary effect related to the drug was obsd. A phase 3 international clin. trial is currently being performed in tamoxifen failure patients where EM-800 (SCH 57050) is compared to Arimidex. The detailed information obtained at the preclin. level with EM-652 or EM-800 indicates that these orally active compds. are highly potent and pure antiestrogens in the mammary gland and endometrium while they prevent bone loss and lower serum cholesterol and triglyceride levels. Preclin. and clin. data clearly suggest the interest of studying this compd.

in the neoadjuvant and adjuvant settings and, most importantly, for the prevention of breast and uterine cancer in which settings they should provide addnl. benefits on bone and lipids.

Answer 5:

Bibliographic Information

Hormonal regulation of proliferation and transforming growth factors gene expression in human endometrial adenocarcinoma xenografts. Gong, Yuewen; Murphy, Leigh C.; Murphy, Liam J. Faculty of Medicine, University of Manitoba, Winnipeg, MB, Can. Journal of Steroid Biochemistry and Molecular Biology (1994), 50(1-2), 13-19. CODEN: JSBBEZ ISSN: 0960-0760. Journal written in English. CAN 121:126060 AN 1994:526060 CAPLUS

Abstract

The authors have previously shown that estrogen and progestins regulate both cellular proliferation and transforming growth factor (TGF) expression in human endometrial adenocarcinoma cells in vitro. In the current study the authors examd. the regulation of TGF-α and -β1 expression in endometrial adenocarcinoma xenografts. Four human endometrial adenocarcinoma cell lines were inoculated into female BALB/c nude mice. Administration of 17β-estradiol (E2) increased tumor size in intact mice inoculated with Ishikawa, HEC-50 and HEC-1B cells but inhibited growth of HEC-1A xenografts. 4-Hydroxy tamoxifen (OH-Tam) had similar effects to E2 in animals carrying Ishikawa and HEC-1A cell xenografts but had no significant effect on growth of HEC-50 or HEC-1B xenografts. In intact

mice inoculated with OH-Tam pellets and Ishikawa cells, the tumors were larger and had lower levels of TGF-α mRNA than in untreated or E2 treated mice. In mice carrying Ishikawa, HEC-50 and HEC-1B cell xenografts none of the hormones or agents tested altered TGF-β1 mRNA levels. In contrast, both E2 and OH-Tam significantly increased xenografts TGF-β1 mRNA levels in HEC-1A xenografts as well as significantly reduced tumor size. Medroxyprogesterone acetate (MPA) had no effect on tumor size of Ishikawa, HEC-1A and HEC-1B cell xenografts but significantly increased the size of HEC-50 xenografts. MPA significantly reduced TGF-α expression in Ishikawa cell xenografts but had no effect in the other cell xenografts. MPA had no effect on TGF-β1 expression in any of the xenografts. These observations demonstrate a discordance between the hormonal effects on TGF expression and cellular proliferation and argue against a major role for the TGFs in regulation of human endometrial adenocarcinoma cell proliferation in vivo.

Answer 6:

Bibliographic Information

The EnDA endometrial adenocarcinoma: an estrogen-sensitive, metastasizing, in vivo tumor model of the rat. Horn, Daniel W.; Vollmer, Guenter; Deerberg, Friedrich; Schneider, Martin R. Res. Lab., Schering AG, Berlin, Germany. Journal of Cancer Research and Clinical Oncology (1993), 119(8), 450-6. CODEN: JCROD7 ISSN: 0171-5216. Journal written in English. CAN 120:241450 AN 1994:241450 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A high percentage of endometrial carcinomas contain estrogen and progesterone receptors. For endocrine therapy of recurrent endometrial carcinoma, only high-dose progestins are in clin. use. As, therefore, the development of new endocrine treatment strategies is of great interest, suitable animal models for this tumor are essential. Up to now, only human tumor xenografts transplanted in immune-deficient nude mice, but no syngeneic in vivo tumor models, have been available. In the present article the authors describe the hormone sensitivity of the EnDA endometrial adenocarcinoma of the DA/Han rat growing as s.c. implants in DA/Han rats and athymic nude mice in serial passage. In both species, the tumor expresses estrogen, but no progesterone receptors. Transplanted in DA/Han rats or nude mice, ovariectomy reduced tumor wt. by 64% and 46% resp. In both species substitution of ovariectomized animals with estradiol restored tumor wts. to intact control levels. Estradiol substitution of intact animals did not further enhance tumor growth. The growth of the primary tumor was inhibited by medroxyprogesterone acetate (MPA) at a dose of 100 mg/kg by 67% and by tamoxifen at a dose of 20 mg/kg by 38%. Lung metastases were regularly seen in both species, although to a lesser extent in nude mice than in DA/Han rats. Tamoxifen treatment did not alter the no. of lung metastases, whereas MPA or ovariectomy produced a significant redn. in the no. of lung metastases. The EnDA endometrial carcinoma of the DA/Han rat with respect to its estrogen sensitivity, estrogen receptor expression, morphol. and metastatic growth, grossly resembles a typical endometrial adenocarcinoma and can therefore be regarded as a useful in vivo exptl. model for the evaluation of new endocrine treatment strategies.

Answer 7:

Bibliographic Information

Regulation and turnover of cellular retinol-binding protein in a xenografted human ovarian tumor. Wahlberg, P.; Fex, G.; Wennerberg, J.; Willen, R. Dep. Oto-Rhino-Laryngol., Univ. Hosp. Lund, Lund, Swed. Anticancer Research (1989), 9(1), 181-7. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 111:5082 AN 1989:405082 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A human ovarian mesodermal (Muellerian) mixed heterologous carcinoma, with a high content of cellular retinol-binding protein (CRBP), was used to study the effects of retinoid and hormonal treatment on tumor CRP content, tumor growth rate, differentiation and turnover of CRBP. Tumor growth in general was accompanied by an increase in the CRBP concn. of the xenografted tumors. This was related to the appearance of more mature epithelial cells, showing CRBP immunoreactivity. The increase in CRBP concn. was more pronounced in retinyl palmitate-treated tumors than in tumor tissue from etretinate-treated mice and controls, suggesting that

CRBP synthesis is under the influence of its ligand. Various hormonal treatments had no influence on the CRBP concn. in these tumor cells. The CRBP turnover was similar to that of the bulk of cellular proteins.

Answer 8:

Bibliographic Information

Progestins initiate a luminal to myoepithelial switch in estrogen-dependent human breast tumors without altering growth. Sartorius Carol A; Harvell Djuana M E; Shen Tianjie; Horwitz Kathryn B Division of Endocrinology, Department of Medicine, University of Colorado Health Sciences Center, Aurora, Colorado 80045-7163, USA. Carol.Sartorius@uchsc.edu Cancer research (2005), 65(21), 9779-88. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 16266999 AN 2005587786 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Although long-term clinical use of progestins is associated with an increased incidence of breast cancers, their role in established cancers is unclear. Estrogens are considered to be the main mitogens in the majority of breast cancers. Whether progesterone affects proliferation and/or differentiation is under debate. To assess the role of progesterone in established breast cancers, we used T47D human breast cancer cells that are estrogen receptor (ER) positive and either progesterone receptor (PR) negative or positive for PRA, PRB, or both. These cells were grown as strictly estrogen-dependent solid tumors in ovariectomized female nude mice. Progesterone or medroxyprogesterone acetate (MPA) alone did not support tumor growth, nor did progesterone or MPA given simultaneously with estrogen significantly alter estrogen-dependent tumor growth. However, treatment of mice bearing ER+PR+ but not ER+PR- tumors with either progesterone or MPA increased expression of the myoepithelial cytokeratins (CK) 5 and 6 in a subpopulation of tumor cells. These CK5+/CK6+ cells had decreased expression of luminal epithelial CK8, CK18, and CK19. We conclude that progestins exert differentiative effects on tumors characterized by transition of a cell subpopulation from luminal to myoepithelial. This may not be beneficial, however, because such a phenotype is associated with poor prognosis.

Answer 9:

Bibliographic Information

Medroxyprogesterone acetate therapy against antiangiogenesis of transplanted ovarian cancer in nude mice. Xie Shou-zhen; Wang Jing; Li De-zhong; Wang Yan Department of Obstetrics and Gynecology, Wuhan General Hospital of Guangzhou Command, Wuhan 430070, China. xieshouzhen@163.com Di 1 jun yi da xue xue bao = Academic journal of the first medical college of PLA (2004), 24(7), 821-3. Journal code: 9426110. ISSN:1000-2588. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Chinese. PubMed ID 15257914 AN 2004355027 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

OBJECTIVE: To investigate the effects of medroxyprogesterone acetate (MPA) on angiogenesis and growth of transplanted human ovarian cancer cells in nude mice. METHODS: Ovarian cancer cell line COCI derived from human ovarian serous adenocarcinoma was transplanted into 30 nude mice, which were then randomized equally into 3 groups consisting of two treatment groups (in which MPA was administered at 60 and 120 mg/kg, respectively, twice a week for 4 weeks) and a control group. Six weeks later, the body mass of the nude mice was recorded and the morphology of tumor cells observed by electron microscope. The microvascular density (MVD) was examined by immunohistochemical staining with anti-human factor VIII antibody. RESULTS: Compared with the control group, the growth inhibitory rate in the two treatment groups were 23.76% and 43.80%, respectively, corresponding to the doses of 60 and 120 mg/kg. MVD of 60 mg/kg MPA group (3.64+/-0.02) and 120 mg/kg MPA group (2.11+/-0.12) was lower than that of the control group

(5.14+/-0.74) (P<0.05 and P<0.01, respectively), and there was also significant difference between the two treatment groups (P<0.01). The morphological changes including compaction and margination of the nuclear chromatin, apoptotic bodies, and cell necrosis were significantly increased in the two treatment groups. CONCLUSIONS: MPA can inhibit the angiogenesis and growth of transplanted human ovarian cancer cells in nude mice in a dose-dependent manner, and its anticancer effect may involve induction of cell apoptosis as the result of its effect against angiogenesis.

Answer 10:

Bibliographic Information

Progestin regulation of human endometrial function. Satyaswaroop P G; Tabibzadeh S Department of Obstetrics and Gynecology, The Milton S. Hershey Medical Center, Hershey, PA 17033, USA Human reproduction (Oxford, England) (2000), 15 Suppl 1 74-80. Journal code: 8701199. ISSN:0268-1161. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 10928420 AN 2001032375 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A well-orchestrated sequence of events enables the human endometrium to become receptive to embryo implantation during a defined period in the menstrual cycle. Ovarian steroids, oestradiol and progesterone, regulate many of these functions in a highly co-ordinated manner. There are no experimental systems for critically examining the regulation of endometrial functions by steroid hormones, especially those responses restricted to the epithelium. Using an experimental xenograft model where the steroid responses of normal endometrium could be predictably recapitulated, the role of progesterone in the regulation of alpha crystallin B in the glandular epithelial cells of human endometrium was established.

Answer 11:

Bibliographic Information

Human prostate tumor growth in athymic mice: inhibition by androgens and stimulation by finasteride. Umekita Y; Hiipakka R A; Kokontis J M; Liao S Ben May Institute for Cancer Research, Department of Biochemistry and Molecular Biology, University of Chicago, IL 60637, USA Proceedings of the National Academy of Sciences of the United States of America (1996), 93(21), 11802-7. Journal code: 7505876. ISSN:0027-8424. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 8876218 AN 97030277 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

When the human prostate cancer cell line, LNCaP 104-S, the growth of which is stimulated by physiological levels of androgen, is cultured in androgen-depleted medium for > 100 passages, the cells, now called LNCaP 104-R2, are proliferatively repressed by low concentrations of androgens. LNCaP 104-R2 cells formed tumors in castrated male athymic nude mice. Testosterone propionate (TP) treatment prevented LNCaP 104-R2 tumor growth and caused regression of established tumors in these mice. Such a tumor-suppressive effect was not observed with tumors derived from LNCaP 104-S cells or androgen receptor-negative human prostate cancer PC-3 cells. 5 alpha-Dihydrotestosterone, but not 5 beta-dihydrotestosterone, 17 beta-estradiol, or medroxyprogesterone acetate, also inhibited LNCaP 104-R2 tumor growth. Removal of TP or implantation of finasteride, a 5 alpha-reductase inhibitor, in nude mice bearing TP implants resulted in the regrowth of LNCaP 104-R2 tumors. Within 1 week after TP implantation, LNCaP 104-R2 tumors exhibited massive necrosis with severe hemorrhage. Three weeks later, these tumors showed fibrosis with infiltration of chronic inflammatory cells and scattered carcinoma cells exhibiting degeneration. TP treatment of mice with LNCaP 104-R2 tumors reduced tumor androgen receptor and c-myc mRNA levels but increased prostate-specific antigen in serum- and prostate-specific antigen mRNA in tumors. Although androgen ablation has been the standard treatment for

metastatic prostate cancer for > 50 years, our study shows that androgen supplementation therapy may be beneficial for treatment of certain types of human prostate cancer and that the use of 5 alpha-reductase inhibitors, such as finasteride or anti-androgens, in the general treatment of metastatic prostate cancer may require careful assessment.

Answer 12:

Bibliographic Information

Effects of tamoxifen, medroxyprogesterone acetate and estradiol on tumor growth and oncogene expression in MCF-7 breast cancer cell line transplanted into nude mice. Mizukami Y; Tajiri K; Nonomura A; Noguchi M; Taniya T; Koyasaki N; Nakamura S; Matsubara F Pathology Section, Kanazawa University Hospital, Japan Anticancer research (1991), 11(3), 1333-8. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1832273 AN 91362404 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The effects of three hormonal agents with a different mechanism of action (tamoxifen [TAM], medroxyprogesterone acetate [MPA] and estradiol [E2]) on tumor growth, differentiation and oncogene expression were evaluated using the estrogen-receptor positive human breast carcinoma cell line MCF-7 transplanted into nude mice. In MCF-7 tumors treated with E2, tumor incidence, mean weight of tumors, 3H-thymidine labelling index, differentiation antigen HMFGM (human milk-fat globule membrane) and ras p21, c-myc, neu oncogene products, the level was significantly increased. On the other hand MPA suppressed all of them. TAM increased the level of c-myc expression and HMFGM antigen, but suppressed the others. This evidence indicates that E2 induces both proliferation and differentiation of MCF-7 tumor cells. MPA suppresses both proliferation and differentiation, and TAM induces differentiation and suppresses proliferation.

Answer 13:

Bibliographic Information

Additive inhibitory effects of an androgen and the antiestrogen EM-170 on estradiol-stimulated growth of human ZR-75-1 breast tumors in athymic mice. Dauvois S; Geng C S; Levesque C; Merand Y; Labrie F Medical Research Council Group in Molecular Endocrinology, CHUL Research Center, Quebec, Canada Cancer research (1991), 51(12), 3131-5. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2039992 AN 91249329 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The effects of the androgen dihydrotestosterone (DHT) and of the androgenic steroid medroxyprogesterone acetate were studied on the growth of human ZR-75-1 breast carcinoma in athymic mice. The possibility of additive inhibitory effects of DHT and the new steroidal antiestrogen N-n-butyl, N-methyl-11-[16' alpha-chloro-3',17' alpha-dihydroxyestra-1',3',5'(10')trien-7' alpha-yl]undecanamide (EM-170) was also investigated on tumor growth. Removal of the high dose 17 beta-estradiol (E2) implants used to optimally stimulate initial ZR-75-1 tumor development in ovariectomized mice led to a progressive decrease in tumor area to 50.2 +/- 8% (SEM) of original tumor size 40 days after E2 deprivation. Additional treatment with the androgen DHT led to a more rapid fall in tumor volume, which already reached 57% of pretreatment values at 11 days. Whereas physiological implants of E2 led to a progressive increase in tumor size to about 180% above original size after 40 days, physiological plasma levels (205 +/- 37.2 pg/ml or approximately 0.67 nM) of DHT completely reversed the stimulatory effect of E2. Similar inhibitory effects on E2-stimulated tumor growth were achieved with the synthetic androgenic steroid medroxyprogesterone acetate. When the steroidal antiestrogen EM-170 at the dose of 30 micrograms/day was used simultaneously with DHT, tumor area was further reduced from 99.0 +/- 9.5% (DHT alone) to 58.8 +/- 18% when both DHT and EM-170 were administered together

for 40 days compared with 169 +/- 22.2% in control E2-stimulated animals. The present data show that the androgen DHT as well as medroxy-progesterone acetate are potent inhibitors of E2-stimulated human ZR-75-1 breast cancer cell growth in vivo. Moreover, the inhibitory effect of DHT can be further increased by addition of the antiestrogen EM-170, thus suggesting the interest of combining these 2 classes of compounds acting, at least partially, through different mechanisms, in order to improve breast cancer therapy in women.

Answer 14:

Bibliographic Information

Experimental local administration of CDDP to in vitro models of gynecological malignant tumors transplanted into nude mice (compared with medroxyprogesterone acetate orally administered). Tateyama I; Hashii K; Natsuyama S; Kanto T; Tominaga T; Kamitani N; Mori T Nippon Gan Chiryo Gakkai shi (1989), 24(5), 1053-66. Journal code: 7505713. ISSN:0021-4671. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2528600 AN 89381558 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In order to develop a new method of administration for CDDP, in vitro models of malignant tumors in the field of gynecology were prepared using two cell lines maintained by the authors, and fundamental experiments on the topical injection of CDDP were carried out. In experimental topical injection of CDDP in tumor-bearing nude mice, the test drug demonstrated an excellent tumor regression effect and an inhibitory effect on tumor growth. In the histopathologic examinations, specific necrosis of tumor cells was observed. It was confirmed that this is a highly safe method, as tissue separation, ulceration, or hemorrhagic lesions attributable to the local administration of CDDP were not observed. In the present study, treatment with oral medroxyprogesterone acetate was also used. At the doses used in this study, however, no inhibitory effect on tumor growth or synergism between medroxyprogesterone acetate and CDDP was observed. Topical injection is an excellent pharmacodynamic method that permits the injection of free platin into the tumor itself or in the boundary area between the tumor and normal tissues, with no loss of the drug, and it is considered a safe and effective mode of local administration. Intra-arterial injection of this drug alone or in conjunction with OK-432 can also be used, even though further studies will be required to determine the optimum dosage and reduce side effects. At present, data are being collected on terminal cancer patients for whom no other therapy is available. In the near future this method of administration is expected to be utilized in the clinical treatment of malignant tumors, be it early tumor or progressive cancer.

Answer 15:

Bibliographic Information

Treatment of advanced and recurrent endometrial carcinoma: correlation of patient response to hormonal and cytotoxic chemotherapy and the response predicted by the subrenal capsule chemosensitivity assay. Stratton J A; Mannel R S; Rettenmaier M A; Berman M L; DiSaia P J University of California at Irvine, Medical Center, Orange 92668 Gynecologic oncology (1989), 32(1), 55-9. Journal code: 0365304. ISSN:0090-8258. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2535831 AN 89079087 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The tumors from 38 patients with advanced or recurrent endometrial carcinoma were assayed by the subrenal capsule xenograft assay (SRCA) for sensitivity to hormonal and cytotoxic chemotherapy. Three patients initially received radiation therapy. All other patients received maximal surgical debulking followed by treatment with radiation therapy (5), and/or hormonal (19), and cytotoxic (30) chemotherapy. All the patients who received hormonal chemotherapy had

progression of disease. There were 2 complete responses, 5 partial responses, and 26 disease progressions with cytotoxic chemotherapy; and 2 complete responses, 2 partial responses, and 5 disease progressions with radiation therapy. The SRCA was 100% predictive of the response of the tumors to hormonal therapy and had 75% sensitivity, 65% specificity, and 66% efficiency of the response of the tumors to cytotoxic chemotherapy. Laboratory assays of tumor response to radiation therapy were not measured. Those patients with early stage, well-differentiated tumors with no residual disease had the longest survival times. Absence of residual disease after the first surgery was the most important delineator of survival for all categories of patients.

Answer 16:

Bibliographic Information

Nude mouse system in the study of tumor biology, treatment strategies and progesterone receptor physiology in human endometrial carcinoma. Satyaswaroop P G; Zaino R; Clarke C L; Mortel R Department of Obstetrics and Gynecology, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey 17033 Journal of steroid biochemistry (1987), 27(1-3), 431-8. Journal code: 0260125. ISSN:0022-4731. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 2961935 AN 88092512 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A nude mouse system where the biological, morphological and biochemical characteristics of human endometrial carcinoma are maintained during serial transplantation has been previously described. Applications of this system to the study of (a) hormonal sensitivity (b) treatment strategies and (c) progesterone receptor physiology of human endometrial carcinomas are presented here.

Answer 17:

Bibliographic Information

Experimental combined hormone therapy on human breast carcinomas serially transplanted into nude mice. Fukutomi T; Kubota T; Ikeda T; Isobe Y; Kikuyama S; Shimada A; Nakamura A; Nishiumi T; Enomoto K; Ishibiki K; + Japanese journal of cancer research : Gann (1986), 77(1), 92-7. Journal code: 8509412. ISSN:0910-5050. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2937762 AN 86167767 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Experimental combined hormone therapy with tamoxifen, aminoglutethimide and medroxyprogesterone acetate was investigated using three hormone-dependent human breast carcinomas serially transplanted into nude mice. The antitumor effect of combined tamoxifen and aminoglutethimide was better than that of either tamoxifen or aminoglutethimide alone. Since aminoglutethimide significantly reduced the level of estrogen and the uterine weight in normal female mice, the antitumor effect of combined tamoxifen and aminoglutethimide was assumed to be a result of the low estrogen level produced by aminoglutethimide, favoring the competition of tamoxifen with estrogen receptors. There was no additive antitumor effect of the combination of tamoxifen and medroxyprogesterone acetate, although serum medroxyprogesterone acetate levels in nude mice were almost equivalent to those of humans. These results indicate that combination hormone therapy, especially with and aminoglutethimide, might be a promising method for clinical application.

Answer 18:

Bibliographic Information

Human uterine endometrium and endometriotic tissue transplanted into nude mice. Morphologic effects of various steroid hormones. Bergqvist A; Jeppsson S; Kullander S; Ljungberg O The American journal of pathology (1985), 121(2), 337-41. Journal code: 0370502. ISSN:0002-9440. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 4061568 AN 86048064 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In a study of the morphologic effects of various steroid hormones on human uterine endometrium and endometriotic tissue, specimens from 6 women were transplanted subcutaneously into 24 nude mice. In each case, specimens collected simultaneously were transplanted to 4 mice, endometrium to one lateral abdominal wall and endometriotic tissue to the other. All mice were given polyestradiol phosphate subcutaneously the first day after operation. After a 2-week interval, of each 4 mice, 1 mouse was given polyestradiol phosphate, 1 medroxyprogesterone acetate, 1 danazol, and 1 no further injections. This treatment continued for 8 weeks, after which the mice were killed and the grafts extirpated. Histologic changes in the grafts varied according to the treatment schedule but were very similar in both types of tissue. Our findings suggest that histologic differences between endometrium and endometriotic tissue seen under natural conditions may, at least partly, be due to variations in environmental factors.

Answer 19:

Bibliographic Information

Human endometrium transplanted into nude mice. Histologic effects of various steroid hormones. Bergqvist A; Jeppsson S; Kullander S; Ljungberg O The American journal of pathology (1985), 119(2), 336-44. Journal code: 0370502. ISSN:0002-9440. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3158210 AN 85196383 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In a histologic study of human endometrium transplanted into nude mice, eutopic endometrium from each of 8 women was transplanted subcutaneously to 4 nude mice, 1 of which was treated with polyestradiol phosphate, 1 with MPA, 1 with danazol, and 1 of which was left untreated as a control. Grafts were removed after varying intervals of up to 57 days. Residual histologically evaluable endometrial tissue was found in 32 of the 96 grafts (33%). None of the extirpated grafts had the same histologic pattern as the eutopic endometrium. Besides confirming that human endometrium can be transplanted into nude mice, our findings suggest that grafts react histologically in the same way as eutopic human endometrium to hormone treatment. The specific stroma seems to be crucial to a graft's capacity to respond to hormonal stimuli, and its replacement by fibrous tissue was accompanied by glandular epithelial changes very similar to those seen in human endometriotic lesions.

Answer 20:

Bibliographic Information

Human endometrial carcinomas serially transplanted in nude mice and established in continuous cell lines. Merenda C; Sordat B; Mach J P; Carrel S International journal of cancer. Journal international du cancer (1975), 16(4), 559-70. Journal code: 0042124. ISSN:0020-7136. (COMPARATIVE STUDY); (IN VITRO); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1176207 AN 76024165 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Three out of five human endometrial carcinomas were successfully grafted into nude mice (BALB/c/nu/nu). Two of these tumors could be maintained by serial transplantation. The morphological characteristics displayed by the grafted tumors were comparable to those of the original carcinomas. Permanent cell lines were established from these two tumors. Reinjection of cells grown in vitro into nude mice produced nodules of identical histology as compared to original solid transplants. The influence of medroxyprogesterone acetate on tumor growth in vivo and cell proliferation in vitro was studied. This hormonal treatment did not produce any significant effect on tumor cells, either in vitro or in vivo, for the two endometrial carcinomas. After medroxyprogesterone administration, a slight but non-significant growth inhibition of the tumor cells in vitro was observed and the tumor transplants in vivo did not appear to be influenced. The experiments illustrate the possible use of this model for testing potential anti-cancer agents.